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Influences of Obesity and Bariatric Surgery on the Clinical and Pharmacologic Profile of Rivaroxaban

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Running Head: Rivaroxaban in Obesity and Post-Bariatric Surgery

Key words: Obesity, anticoagulants, bariatric surgery, rivaroxaban, thromboprophylaxis

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ABSTRACT

The health implications of obesity are myriad and multifaceted. Physiologic changes associated with obesity can affect the absorption, distribution, metabolism, and excretion of administered drugs, thereby altering their pharmacologic profiles. In 2016, the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis published recommendations regarding the use of direct oral anticoagulants (DOACs) in obese patients. This guidance provides uniform recommendations for all DOACs, yet data suggest that individual agents may be affected to different degrees by obesity. Moreover, there are no recommendations currently available to guide DOAC use in bariatric surgery patients, in whom anatomic and physiologic changes to the digestive system can influence drug pharmacokinetics. Our review of the available literature indicates that the clinical profile of the DOAC rivaroxaban is not affected by high weight or bariatric surgery; hence, it does not appear that rivaroxaban dosing needs to be altered in these patient populations.

INTRODUCTION

An estimated 13% of the world's population is currently obese (body mass index [BMI] ≥30 kg/m^2), and the incidence is increasing along with the associated health and economic burden.[1] Obesity has multifaceted impacts on approaches to patient health and disease management, including selection of anticoagulant therapy. Considered a prothrombotic and proinflammatory state,[2] obesity is a risk factor for conditions where anticoagulant therapy is indicated (eg, hip/knee replacement,[3] atrial fibrillation,[4] venous thromboembolism[5]). Beyond inducing a prothrombotic state, obesity may influence thrombotic risk through its effects on the clinical pharmacology (pharmacokinetics/pharmacodynamics) of anticoagulants, potentially leading to either undercoagulation or overcoagulation, thereby increasing the risk for thrombotic or bleeding events.

Best practices regarding the use of anticoagulants in obese patients remain to be determined. The emergence of direct oral anticoagulants (DOACs) broadens the anticoagulant treatment armamentarium, but DOAC use in morbidly obese patients (BMI ≥40 kg/m^2) has been called into question. In 2016, the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis (ISTH) published a guidance that included a suggestion to not use DOACs in patients with a BMI >40 kg/m^2 or weight >120 kg due to limited clinical data and concerns regarding the potential effects of weight extremes on the pharmacology of these agents.[6] If DOACs are used in these patients, the ISTH guidance suggests monitoring drug-specific peak and trough levels. The ISTH recommendations apply to

all DOACs, although evidence suggests that their clinical and pharmacologic profiles may not be influenced to the same extent by weight.[7]

One consequence of the obesity epidemic is the rapidly growing use of bariatric surgery. Bariatric surgery, which involves restricting the functional size of the stomach and/or inducing nutrient malabsorption, has shown favorable results for reducing weight and can produce improvements in obesity-related co-morbidities.[8,9] From a drug-delivery standpoint, a history of bariatric surgery is worth consideration because the accompanying anatomic and physiologic changes[10] may affect drug pharmacokinetics, thereby potentially influencing efficacy and safety.[8,9] Understanding changes in response to anticoagulant therapy after bariatric surgery is essential due to the elevated thrombotic risk in this patient population.[11] Little is known, however, regarding the pharmacology of DOACs after bariatric surgery, both in the immediate postoperative period and during long-term therapy.

Rivaroxaban is a DOAC that has been extensively studied in a variety of clinical indications, including those with a high likelihood of comorbid obesity. Rivaroxaban has also been studied in a small number of healthy subjects both before and following bariatric surgery. The purpose of this review is to assess the available evidence for use of rivaroxaban in the context of obesity or bariatric surgery by examining the published literature for studies that have evaluated the clinical or pharmacologic profile of rivaroxaban in these patient populations.

METHODS

Articles for inclusion in this review were identified from the published literature by interrogation of the MEDLINE database and by search of abstracts from relevant scientific congresses. Search terms included pharmacokinetics, pharmacodynamics, obese, obesity, overweight, body weight, BMI, bariatric surgery, and gastric bypass in conjunction with rivaroxaban/BAY 59-7939. In addition, reference lists from included publications were used to identify other articles of interest. All publications pertinent to the subject matter were included in the manuscript; no exclusions based on study criteria or date of publication were applied.

RIVAROXABAN AND OBESITY

The extent of drug exposure is dependent on its absorption, distribution, metabolism, and excretion. There is evidence to suggest that each of these components may be influenced by obesity.[9] However, whether or not drug exposure is affected to a measurable or clinically meaningful degree is agent specific. In the case of rivaroxaban, pivotal clinical trials, clinical pharmacology studies, and population models provide insights into the impact of obesity on drug exposure.

Pharmacokinetic/Pharmacodynamic Studies

A clinical pharmacology study was conducted to assess the influence of weight extremes on the general safety and pharmacologic profile of rivaroxaban after a single 10-mg oral dose.[12] The study enrolled 48 healthy subjects and compared results in subjects in weight categories of ≤50 kg (low weight), 70-80 kg (normal weight), and >120 kg (high weight). No differences in safety were observed among weight groups. The pharmacokinetic profile of rivaroxaban was comparable in subjects in the normal- and high -weight groups (**Figure 1**),[12] and the time course of factor Xa activity inhibition by rivaroxaban was largely unaffected by weight (**Figure 2**).[12] The authors concluded that the overall limited influence of weight on the pharmacologic profile of rivaroxaban (ie, generally <15% change compared with normal weight) makes it unlikely that dose adjustment is necessary for patients with weight extremes. This study formed the basis for the current rivaroxaban prescribing information, which does not suggest dose adjustment based on weight.[13]

Insights into the influence of weight on the pharmacology of rivaroxaban in more

diverse patient populations have been obtained through population modeling conducted using data from multiple clinical trials in various indications. Two publications have reported on the population pharmacokinetics/pharmacodynamics of rivaroxaban in patients who had undergone total hip/knee arthroplasty.[14,15] The included studies set a lower weight limit (45 kg) but no upper bound. Reported weights of enrolled patients ranged from 45 kg to as much as 120 to 125 kg (hip studies) or 173 kg (knee study). The only notable effect of weight on rivaroxaban pharmacokinetics was a modest influence on volume of distribution. Weight was identified as a covariate that influenced rivaroxaban-mediated inhibition of factor Xa activity; however, the magnitude of effect was small and not considered to be clinically relevant.[15]

Mueck[16] subsequently published population pharmacokinetics using data from two phase 2 studies of rivaroxaban in the treatment of acute deep vein thrombosis. These studies excluded patients weighing <45 kg, but had no upper weight/BMI threshold. The only rivaroxaban pharmacokinetic parameter influenced by weight was the volume of distribution, the effects on which were moderate and within observed interindividual variability. Weight did not have a significant effect on the relationship between rivaroxaban pharmacologic parameters. In a more recent population pharmacokinetic publication that analyzed data from the ROCKET AF study, lean body mass (but not body weight/fat) affected the apparent volume of distribution of rivaroxaban.[17] The influence of lean body mass on the volume of distribution was modest and within the range of interindividual variability.

Together, these analyses indicate that high weight/BMI does not have a clinically meaningful impact on the pharmacology of rivaroxaban. Volume of distribution was the

parameter most likely to be influenced by high weight/BMI, although it is important to note that this difference was within the observed range of interpatient variability.

Efficacy and Safety

The efficacy and safety of rivaroxaban have been evaluated in several large trials across multiple indications, including prophylaxis in patients undergoing total hip/knee arthroplasty, treatment of acute venous thromboembolism and prevention of venous thromboembolism recurrence, and stroke prevention in atrial fibrillation. These trials included a considerable proportion of patients in high weight/BMI categories (**Table 1**),[18-21] which allowed for weight/BMI-based subgroup analyses.

Total Hip or Knee Arthroplasty. The RECORD series of pivotal clinical studies evaluated venous thromboembolism prevention with rivaroxaban versus enoxaparin in patients who had undergone total hip/knee arthroplasty.[22-25] Turpie[21] published a pooled analysis of the 4 RECORD studies that included data from 12,279 patients who received either rivaroxaban 10 mg daily or enoxaparin 40 mg once daily (or 30 mg every 12 hours). No weight or BMI limits were imposed for study inclusion, resulting in considerable representation of patients weighing >90 kg (**Table 1**).[18-21] In the overall cohort, the primary efficacy endpoint (composite of symptomatic venous thromboembolism and all-cause mortality) occurred significantly less frequently among those treated with rivaroxaban versus enoxaparin (0.5% and 1.0%, respectively; *P*=0.001). Reductions in the composite primary efficacy endpoint were consistent when analyzed by weight subgroup (≤70, >70 to 90, and >90 kg) (**Figure 3**),[21] suggesting that the observed

benefits of rivaroxaban may also be applicable to patients with high weight. For the overall cohort, the rates of major plus clinically relevant nonmajor bleeding were comparable in patients who received rivaroxaban (2.8%) or enoxaparin (2.5%; *P* = 0.19). These findings were maintained across weight strata (**Figure 4**).[21]

Friedman et al (2013)[26] subsequently published a retrospective analysis of the RECORD studies to determine whether complication rates after total hip/knee arthroplasty are elevated among patients who are morbidly obese. No increase in the incidences of asymptomatic/symptomatic deep vein thrombosis, symptomatic pulmonary embolism, any bleeding, or major or clinically relevant nonmajor bleeding were observed among patients who were morbidly obese (n=445) relative to patients with a BMI <40 kg/m^2 (n=11,910). Overall, the totality of evidence indicates that the efficacy and safety of rivaroxaban among patients undergoing orthopedic surgery is not adversely affected by high weight/obesity.

Stroke Prevention in Atrial Fibrillation. Rivaroxaban was studied for the prevention of stroke in patients with nonvalvular atrial fibrillation in the pivotal ROCKET AF clinical trial.[20] Patients in ROCKET AF (N=14,264) received rivaroxaban 20 mg daily (15 mg daily in patients with creatinine clearance of 30-49 mL/min) or adjusted-dose warfarin (target International Normalized Ratio [INR], 2.0-3.0). Weight was not a study enrollment criterion. More than one-quarter of patients weighed >90 kg at baseline (**Table 1**).[18-21] The per-protocol and intention-to-treat analyses demonstrated noninferiority of rivaroxaban versus warfarin for the primary endpoint (composite of stroke or systemic embolism), with consistently lower event rates in the rivaroxaban

group. Noninferiority of rivaroxaban was maintained across weight/BMI strata (**Figure 3**).[20] Interestingly, the lowest event rates were observed in the highest weight/BMI categories for both treatment groups. A *post hoc* analysis of ROCKET AF data found that the rates of the primary endpoint were significantly lower in overweight (hazard ratio [95% confidence interval (CI)]: 0.79 [0.64-0.98]; *P*=0.029) and obese patients (0.66 [0.53-0.84]; *P*≤0.001) in comparison with normal-weight patients.[27]

In the overall ROCKET AF cohort, the rates of major and clinically relevant nonmajor bleeding were similar in patients receiving rivaroxaban or warfarin.[20] However, significantly lower rates of intracranial hemorrhage (0.5% and 0.7% per year; *P*=0.02) and fatal bleeding (0.2% and 0.5% per year; *P*=0.003) were observed in the rivaroxaban group. Safety outcomes in the rivaroxaban and warfarin arms, including rates of major and clinically relevant nonmajor bleeding (**Figure 4**),[20] were consistent across weight/BMI subgroups. The lack of significant effect of obesity on the efficacy and safety of rivaroxaban in the context of stroke prevention in atrial fibrillation suggests that the pharmacologic profile of this agent in obese and non-obese subjects is likely similar.

Venous Thromboembolism. Two large, pivotal clinical trials assessed the efficacy and safety of rivaroxaban for the treatment of acute symptomatic deep vein thrombosis (EINSTEIN-DVT) or pulmonary embolism (EINSTEIN-PE).[18,19] In both studies, patients were randomly assigned to rivaroxaban (15 mg twice daily for 3 weeks, followed by 20 mg once daily) or enoxaparin followed by a vitamin K antagonist (VKA) for 3, 6, or 12 months. An extension study allowed an additional 6 or 12 months of treatment for qualifying patients. No limitations were placed on enrollment based on weight/BMI.

Across studies and treatment arms, ~14% of patients weighed >100 kg (**Table 1**).[18-21] For the primary efficacy endpoint, symptomatic recurrent venous thromboembolism, rivaroxaban was found to be noninferior to enoxaparin/VKA therapy in EINSTEIN-DVT and EINSTEIN-PE. Rates of major and clinically relevant nonmajor bleeding (the primary safety endpoint) were equivalent between groups in EINSTEIN-DVT (8.1% for both) and slightly lower with rivaroxaban versus enoxaparin/VKA therapy in EINSTEIN-PE (10.3% and 11.4%, respectively; *P*=0.23). Results for the primary efficacy and safety endpoints were consistent across weight subgroups.

A recently published *post hoc* analysis of pooled data from the EINSTEIN-DVT and EINSTEIN-PE studies detected no association between weight/BMI and risk of recurrent venous thromboembolism, major bleeding, or composite of major bleeding and clinically relevant nonmajor bleeding in patients who received rivaroxaban.[28] Hazard ratios for the comparison of rivaroxaban and enoxaparin/VKA therapy were consistent across weight/BMI subgroups (**Figures 3 and 4**).[28]

Pivotal randomized controlled trial data, although informative for guiding clinical practice, may have limited relevance to real-world patient populations. Data from everyday practice are, therefore, valuable in providing a perspective on drug efficacy and safety in a more diverse patient population. One such study that evaluated the effect of weight extremes on the pharmacokinetics, efficacy, and safety of rivaroxaban in the treatment of venous thromboembolism was recently reported.[29] In this unselected group of 219 patients, rivaroxaban plasma concentrations were comparable between patients weighing 50-120 kg (median [95% CI]: 308 [308-381] ng/mL) and those weighing more than 120 kg (281 [242-327] ng/mL), but were significantly higher in

patients weighing less than 50 kg (460 [380-601] ng/mL; *P*=0.005 for the comparison with the 50-120 kg and >120 kg groups). The rates of recurrent venous thromboembolism, major bleeding, and clinically relevant bleeding were similar across the weight groups, and higher plasma levels of rivaroxaban in patients weighing <50 kg were not associated with increased bleeding or recurrent venous thromboembolism. These results further support the observed lack of effect of high weight on the clinical profile of rivaroxaban that was observed in clinical trials in patients with venous thromboembolism.

RIVAROXABAN AND BARIATRIC SURGERY

The influence of bariatric surgery on drug pharmacology, efficacy, and safety is largely unknown, as few studies have examined this question. Theoretically, bariatric surgery has potential to influence pharmacokinetics of administered drugs via a multitude of mechanisms, including changes in gastric emptying time, decreased small intestine transit time, and reduced intestinal surface area.[8,9] The net result of anatomic and physiologic changes on drug pharmacokinetics is highly dependent on the nature of the bariatric surgery, route of drug administration, and characteristics of the individual drug.

There is some precedent for bariatric surgery influencing the pharmacology and clinical profile of anticoagulants. Vitamin K deficiency has been reported after gastric bypass surgery,[30] which may significantly impact the anticoagulant effects of VKA agents such as warfarin. Functional consequences in terms of poor INR control and resulting clinical complications have been observed with VKA use after gastric bypass.[31-36]

Initial data on the pharmacology of rivaroxaban in patients who had undergone bariatric surgery were reported in case studies. Mahlmann et al[34] described a patient who experienced unstable INR during VKA therapy after undergoing gastric bypass. The patient was considered to be at high risk for venous thromboembolism due to prior events and, therefore, required continued anticoagulation. After switching to rivaroxaban 20 mg once daily, plasma drug concentrations, INR, and activated partial thromboplastin time were measured. Following the first rivaroxaban dose, plasma drug concentrations increased rapidly, reaching peak values that were within the expected

range. The authors concluded that “resorption of rivaroxaban is not significantly impaired by bariatric surgery.” Similar results were reported by Cintineo[37] for a patient with atrial fibrillation and history of gastric bypass who experienced a transient ischemic attack 3 years after surgery and was subsequently put on rivaroxaban 20 mg daily.

New data provide insights on the pharmacology of rivaroxaban in the immediate postoperative period. A single-center clinical trial evaluated pharmacokinetics of rivaroxaban 10 mg administered 1 day before and 3 days after surgery in morbidly obese patients scheduled to undergo bariatric surgery.[38] Twelve patients were assessed: 6 underwent Roux-en-Y gastric bypass and 6 underwent sleeve gastrectomy. The preoperative data revealed area under the plasma concentration-time curve (AUC) values in this obese population that were comparable with those reported after administration of rivaroxaban 10 mg in healthy volunteers and patients who had undergone hip replacement.[14,39] A slight increase in AUC was observed after bariatric surgery in the overall study population; the difference compared with the preoperative measurement was more apparent among patients who underwent sleeve gastrectomy than in those who underwent Roux-en-Y gastric bypass (**Table 2**).[38] The plasma concentration-time curves before and after surgery were largely superimposable for gastric bypass patients, whereas a modest difference in peak rivaroxaban concentration was observed postoperatively in the sleeve-gastrectomy group (**Figure 5**).[38] Nonetheless, the observed differences in pharmacokinetic parameters after bariatric surgery were within the expected range of individual variation. The pharmacodynamic effects of rivaroxaban, as measured by thrombin-antithrombin complexes, prothrombin activation fragments F1+2, and D-dimer concentrations, were consistent with the

pharmacokinetic profile (**Figure 6**).[38] These data support the concept that the pharmacology of a 10-mg dose of rivaroxaban is not significantly affected by bariatric surgery. Additional studies with larger numbers of patients, extended duration of therapy, and higher rivaroxaban doses would be helpful for a more detailed characterization of the rivaroxaban profile.

CLINICAL IMPLICATIONS

The body of clinical evidence does not suggest that dosing adjustments for rivaroxaban are needed for patients with a BMI >40 kg/m^2 or weight of >120 kg. High weight has not been shown to have a clinically meaningful effect on the pharmacology of rivaroxaban, and the efficacy and safety profiles of rivaroxaban in high weight/BMI subgroups were consistently similar to those observed in patients with normal weight/BMI across large pivotal clinical trials in different indications.

The recent guidance from the ISTH advocates the measurement of peak and trough levels of DOACs in patients with a BMI >40 kg/m^2 or weight of >120 kg.[6] This recommendation is based on the assumption that the pharmacology of DOACs will differ between obese and non-obese patients. The evidence presented herein, which includes a study specifically examining the effects of weight on pharmacology,[12] population pharmacokinetic modeling in diverse patient populations,[14-16] and pharmacologic data from morbidly obese patients before and after bariatric surgery,[38] indicates that rivaroxaban's pharmacologic profile in obese or high-weight patients is comparable to that observed in patients with normal weight. Therefore, the routine measurement of plasma concentrations does not appear to be necessary for patients who receive rivaroxaban.

Exploring the influence of bariatric surgery on drug exposure is still in early stages. Although it is well established that the level of anticoagulation achieved with VKA therapy is significantly affected by bariatric surgery, necessitating careful monitoring and dose adjustment,[31-36] less is known regarding the effects of bariatric surgery on the anticoagulant activity of DOACs. For rivaroxaban, the available data

suggest that pharmacokinetic and pharmacodynamic effects of a 10-mg dose of rivaroxaban are not appreciably altered after bariatric surgery. Further study of rivaroxaban, ideally with higher doses, and other DOACs in this patient population is warranted.

In total, the data indicate that dose adjustment is not necessary when administering rivaroxaban to patients who are obese or who have undergone bariatric surgery. Future research should ensure that these populations are adequately represented in clinical trials. Moreover, additional studies are needed to further explore the effects of obesity/bariatric surgery on the pharmacologic profiles of anticoagulant therapies.

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FIGURE LEGENDS

Figure 1. Mean rivaroxaban plasma concentration-time curve after administration of a single 10-mg oral dose. Each weight group included 12 healthy subjects. Reprinted from Kubitza et al (2007).[12]

Figure 2. Influence of body weight on rivaroxaban-mediated (A) median inhibition of factor Xa activity and (B) median prolongation of prothrombin time. Each weight group included 12 healthy subjects who received a single oral dose of rivaroxaban 10 mg. Reprinted from Kubitza et al (2007).[12]

Figure 3. Relative efficacy of rivaroxaban in weight and body mass index subgroups in large phase 3 clinical trials. Odds/hazard ratios and 95% confidence intervals of the primary efficacy endpoint for the comparison of rivaroxaban with enoxaparin (RECORD studies),[21] warfarin (ROCKET AF),[20] or enoxaparin/vitamin K antagonist therapy (EINSTEIN studies).[28]

Figure 4. Relative safety of rivaroxaban in weight and body mass index subgroups in large phase 3 clinical trials. Hazard ratios and 95% confidence intervals of the composite endpoint of major bleeding and clinically relevant nonmajor bleeding for the comparison of rivaroxaban with enoxaparin (RECORD studies),[21] warfarin (ROCKET AF),[20] or enoxaparin/vitamin K antagonist therapy (EINSTEIN studies).[28]

Figure 5. Rivaroxaban plasma concentration-time curve before and after bariatric surgery, stratified by procedure type, following administration of single 10-mg oral doses. Panel A represents patients who underwent Roux-en-Y gastric bypass (n = 6) and panel B represents patients who underwent sleeve gastrectomy (n = 6). Reprinted from Kröll D, et al.[38]

Figure 6. Comparison of pharmacodynamic measures performed following administration of rivaroxaban 10 mg before and after bariatric surgery, stratified by procedure type. Top panels: thrombin-antithrombin complex concentrations; middle panels: prothrombin activation fragment F1+2 concentrations; bottom panels: D-dimer concentrations. Data represent medians and ranges for 6 patients who underwent Roux-en-Y gastric bypass and 5 patients who underwent sleeve gastrectomy. Interpretation of the postoperative results must take into consideration the procoagulant state induced by surgical intervention and the administration of low-molecular-weight heparin the previous day as part of the postoperative standard of care. Reprinted from Kröll D, et al.[38]

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TABLES

Table 1. Characteristics and Weight Category Distributions in Large Phase 3 Clinical Trials With Rivaroxaban

Study *Population*	Treatment	Weight Category Distribution Patients, n (%)			
		≤70 kg	**>70-90 kg**	**>90 kg**	
RECORD studies[21]*	Rivaroxaban 10 mg OD	2093 (33.9)	2669 (43.3)	1409 (22.8)	
Patients scheduled for elective total hip or knee arthroplasty	Enoxaparin 40 mg OD or 30 mg every 12 hours	1988 (32.1)	2732 (44.1)	1474 (23.8)	
ROCKET AF[20]*	Rivaroxaban 20 mg daily†	2013 (28.4)	3031 (42.8)	2035 (28.7)	
Patients with nonvalvular atrial fibrillation at increased risk for stroke	Dose-adjusted warfarin	2012 (28.4)	3135 (44.2)	1942 (27.4)	
		≤50 kg	**>50-100 kg**	**>100 kg**	**Missing**
EINSTEIN DVT[18]	Rivaroxaban 15 mg BID for 3 weeks, then 20 mg OD	37 (2.1)	1443 (83.4)	245 (14.2)	6 (0.3)
Patients with objectively confirmed proximal deep vein thrombosis, without symptomatic pulmonary embolism	Enoxaparin followed by a VKA	49 (2.9)	1422 (82.8)	246 (14.3)	1 (<0.1)
EINSTEIN PE[19]	Rivaroxaban 15 mg BID for 3 weeks, then 20 mg OD	38 (1.6)	2034 (84.1)	345 (14.3)	2 (<0.1)
Patients with acute symptomatic pulmonary embolism with or without deep vein thrombosis	Enoxaparin followed by a VKA	43 (1.8)	2010 (83.3)	359 (14.9)	1 (<0.1)

BID, twice daily; OD, once daily; VKA, vitamin K antagonist.
*Derived from the number of patients included in the subgroup analysis for the primary efficacy endpoint.
†Rivaroxaban dose was 15 mg daily for patient with a creatinine clearance of 30 to 49 mL per minute.

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Table 2. Pharmacokinetic Parameters of Rivaroxaban Before and After Bariatric Surgery

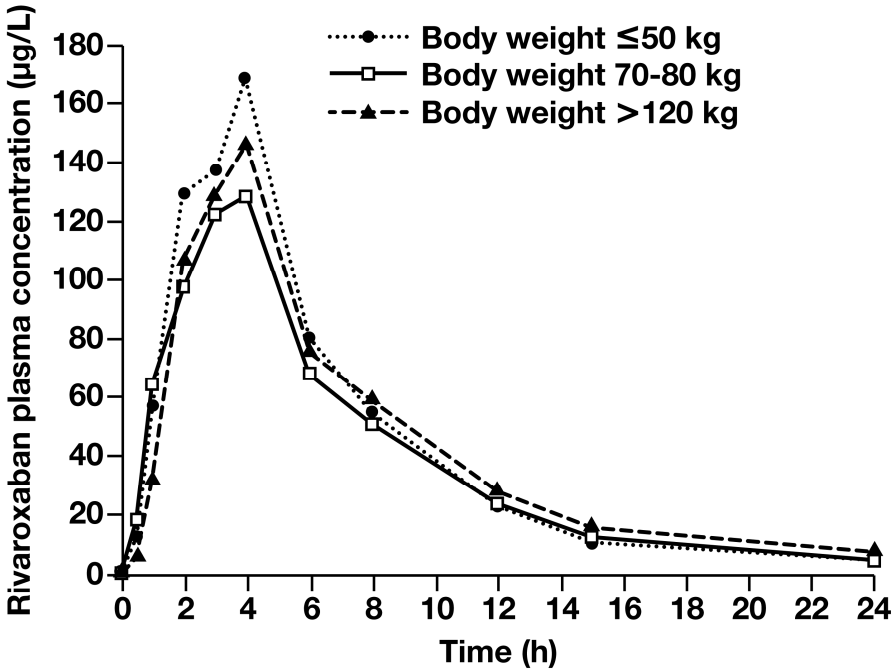
Parameter*	Before Surgery	After Surgery	Ratio†
All patients pooled			
AUC (µg • h/L)	952.6 / 16.8	1095.5 / 16.8	0.87 [0.77-0.98]
C_{max} (µg/L)	135.9 / 19.3	137.3 / 33.3	0.99 [0.79-1.24]
$t_{1/2}$ (h)	13.5 / 38.8	11.6 / 58.7	1.16 [0.82-1.64]
V_Z/f (L/kg)	47.9 / 22.3	44.4 / 26.1	1.08 [0.99-1.18]
t_{max} (h)	1.5 (0.9-4)	2 (1-4)	NA
Roux-en-Y gastric bypass			
AUC (µg • h/L)	933.7 / 22.3	1029.4 / 7.4	0.91 [0.75-1.09]
C_{max} (µg/L)	136.5 / 10.7	110.8 / 31.8	1.23 [0.91-1.66]
$t_{1/2}$ (h)	13.8 / 46.6	15 / 60.0	0.92 [0.57-1.48]
V_Z/f (L/kg)	55.3 / 22.5	52.7 / 20.8	1.05 [0.91-1.21]
t_{max} (h)	1.5 (0.9-4)	2.5 (1-4)	NA
Sleeve gastrectomy			
AUC (µg • h/L)	971.9 / 10.6	1165.8 / 21.9	0.83 [0.68-1.02]
C_{max} (µg/L)	135.3 / 26.7	170.0 / 15.9	0.80 [0.59-1.08]
$t_{1/2}$ (h)	13.1 / 34.1	8.9 / 44.6	1.47 [0.82-2.64]
V_Z/f (L/kg)	41.5 / 9.5	37.4 / 18.1	1.11 [0.95-1.29]
t_{max} (h)	1.5 (1-4)	1.5 (1-4)	NA

AUC, area under the plasma concentration-time curve from time 0 to infinity; C_{max}, peak plasma concentration; $t_{1/2}$, terminal half-life; t_{max}, time to peak plasma concentration; Vz/f, (Dose/C_0)/body weight apparent volume of distribution during the terminal phase divided by total body weight (in kg).

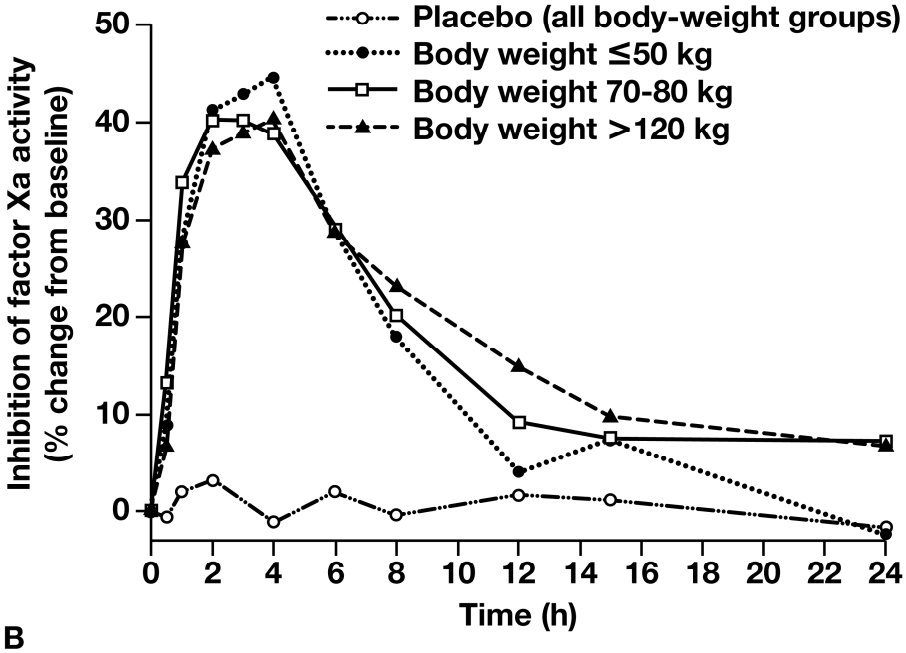
*Data are geometric mean/coefficient of variation, except for t_{max}, which is presented as median (range).

†Ratio of before/after surgery and 95% confidence interval.

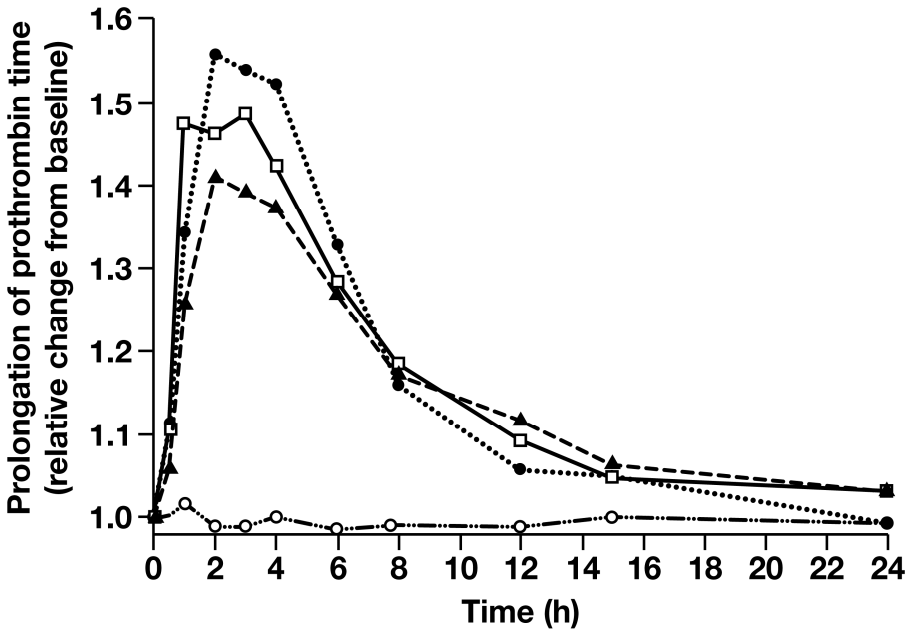
Reprinted from Kröll D, et al.[38]

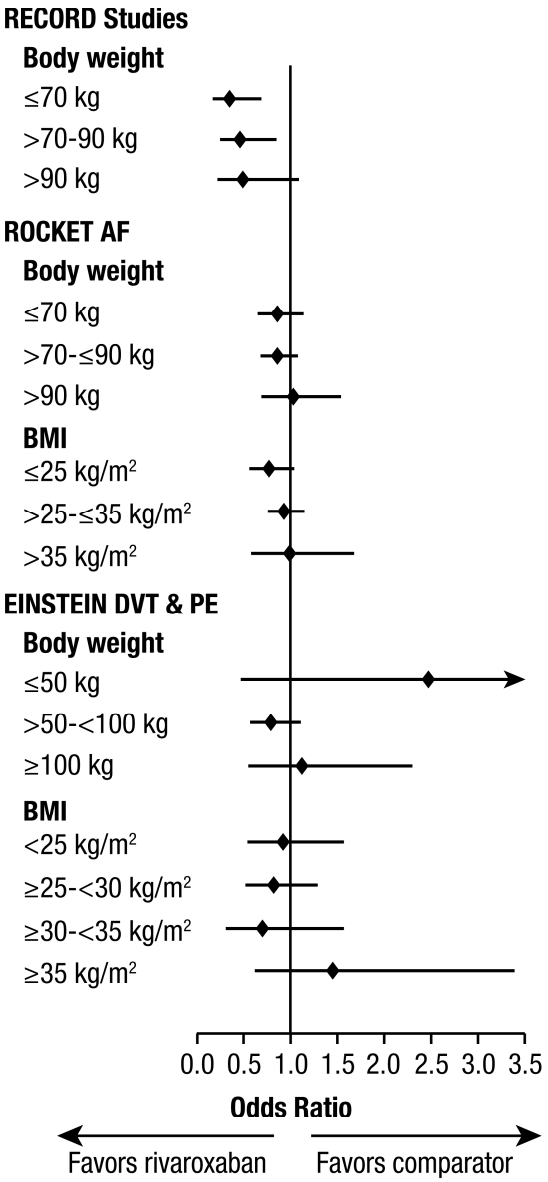


A

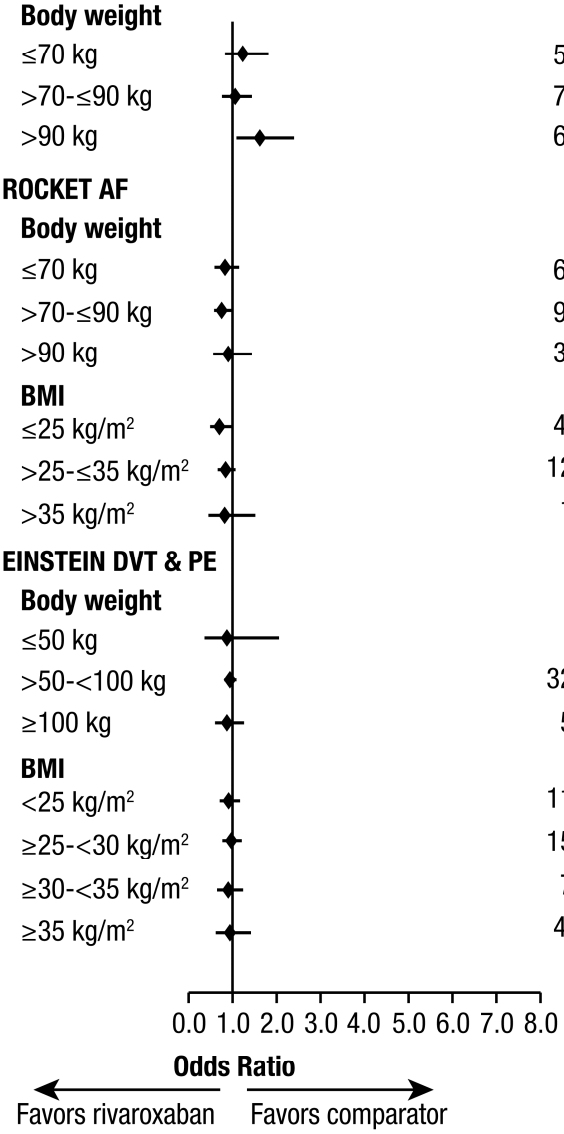

Placebo (all body-weight groups)
Body weight ≤50 kg
Body weight 70-80 kg
Body weight >120 kg
Inhibition of factor Xa activity
(% change from baseline)
50
40
30
20
10
0
0 2 4 6 8 10 12 14 16 18 20 22 24
Time (h)

B

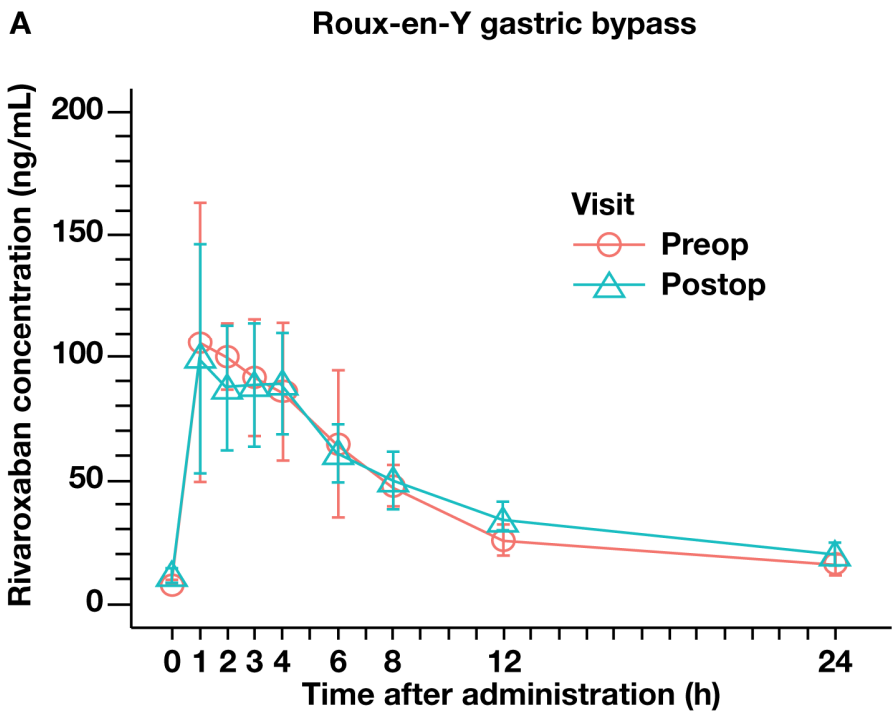

Prolongation of prothrombin time
(relative change from baseline)
1.6
1.5
1.4
1.3
1.2
1.1
1.0
0 2 4 6 8 10 12 14 16 18 20 22 24
Time (h)

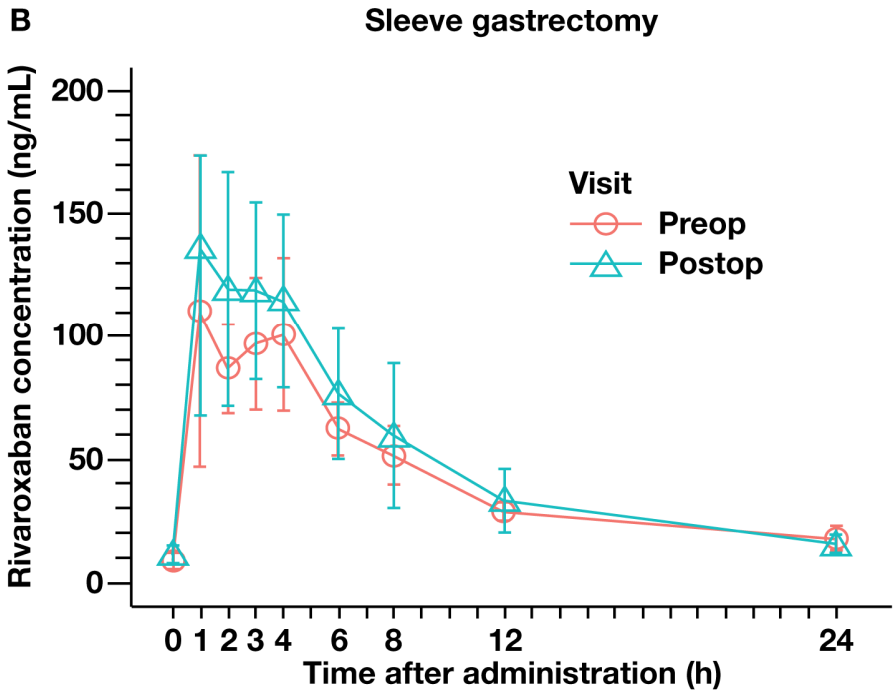


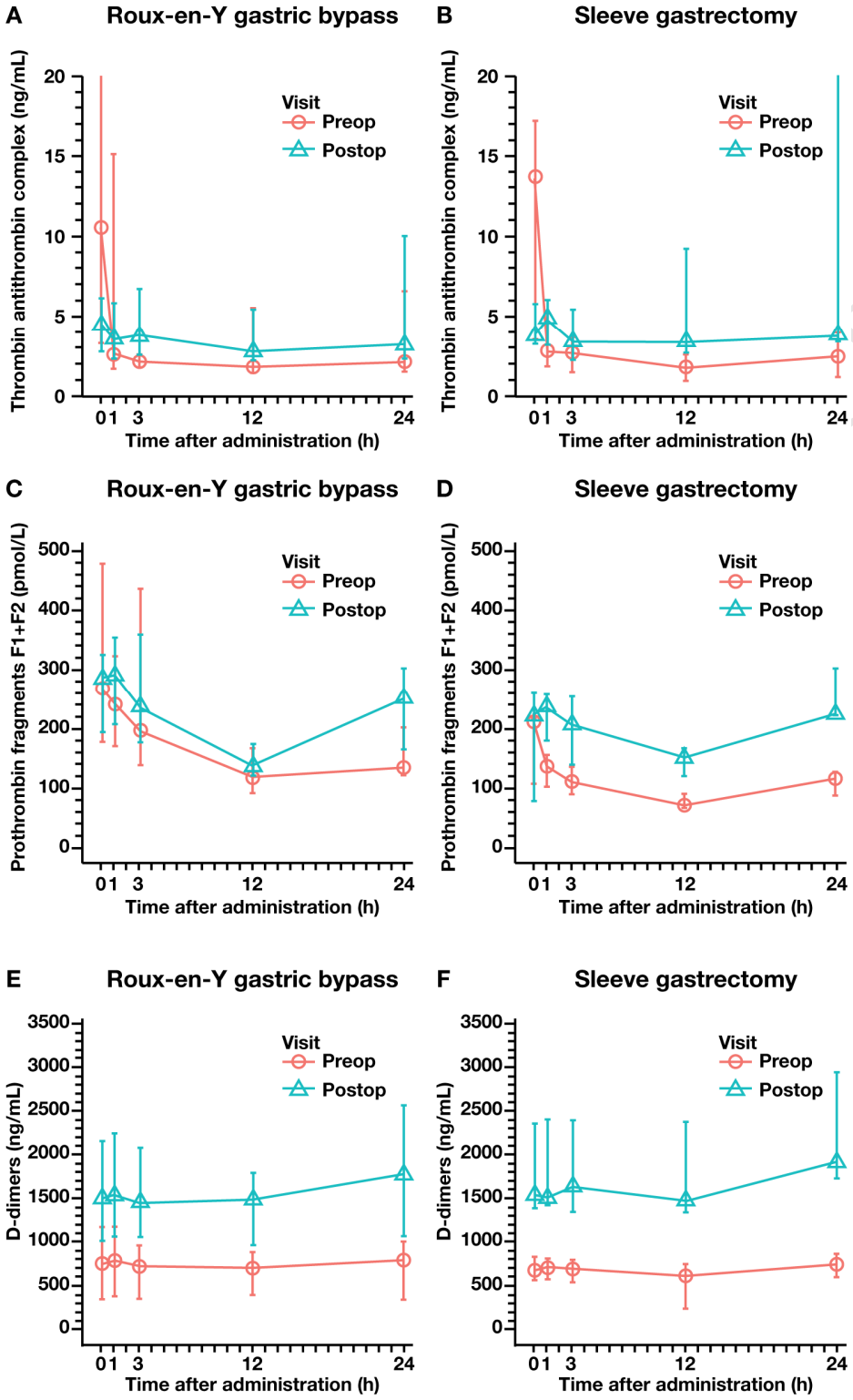
	Rivaroxaban	Comparator
RECORD Studies		
Body weight		
≤70 kg	11/2093 (0.5%)	30/1988 (1.5%)
>70-90 kg	15/2669 (0.6%)	33/2732 (1.2%)
>90 kg	9/1409 (0.6%)	19/1474 (1.3%)
ROCKET AF		
Body weight		
≤70 kg	93/2013 (4.6%)	109/2012 (5.4%)
>70-≤90 kg	126/3031 (4.2%)	151/3135 (4.8%)
>90 kg	50/2035 (2.5%)	46/1942 (2.4%)
BMI		
≤25 kg/m²	72/1695 (4.3%)	98/1750 (5.6%)
>25-≤35 kg/m²	169/4409 (3.8%)	180/4417 (4.1%)
>35 kg/m²	28/972 (2.9%)	27/919 (2.9%)
EINSTEIN DVT & PE		
Body weight		
≤50 kg	5/75 (6.7%)	2/92 (2.2%)
>50-<100 kg	65/3369 (1.9%)	79/3342 (2.4%)
≥100 kg	16/698 (2.3%)	14/695 (2.0%)
BMI		
<25 kg/m²	28/1266 (2.2%)	30/1215 (2.5%)
≥25-<30 kg/m²	35/1608 (2.2%)	41/1650 (2.5%)
≥30-<35 kg/m²	10/825 (1.2%)	14/805 (1.7%)
≥35 kg/m²	13/427 (3.0%)	9/434 (2.1%)



RECORD Studies	Rivaroxaban	Comparator
Body weight		
≤70 kg	57/2093 (2.7%)	44/1988 (2.2%)
>70-≤90 kg	76/2669 (2.8%)	74/2732 (2.7%)
>90 kg	62/1409 (4.4%)	40/1474 (2.7%)
ROCKET AF		
Body weight		
≤70 kg	63/2004 (3.1%)	78/2008 (3.9%)
>70-≤90 kg	92/3022 (3.0%)	129/3133 (4.1%)
>90 kg	34/2033 (1.7%)	36/1940 (1.9%)
BMI		
≤25 kg/m^2	49/1685 (2.9%)	75/1745 (4.3%)
>25-≤35 kg/m^2	121/4400 (2.8%)	145/4415 (3.3%)
>35 kg/m^2	19/971 (2.0%)	22/918 (2.4%)
EINSTEIN DVT & PE		
Body weight		
≤50 kg	9/75 (12.0%)	13/91 (14.3%)
>50-<100 kg	325/3352 (9.7%)	339/3333 (10.2%)
≥100 kg	53/696 (7.6%)	60/691 (8.7%)
BMI		
<25 kg/m^2	119/1257 (9.5%)	123/1214 (10.1%)
≥25-<30 kg/m^2	152/1603 (9.5%)	160/1643 (9.7%)
≥30-<35 kg/m^2	70/822 (8.5%)	77/803 (9.6%)
≥35 kg/m^2	45/426 (10.6%)	47/432 (10.9%)


A
Roux-en-Y gastric bypass
Rivaroxaban concentration (ng/mL)
200
150
100
50
0
Visit
Preop
Postop
0 1 2 3 4 6 8 12 24
Time after administration (h)


B
Sleeve gastrectomy
Rivaroxaban concentration (ng/mL)
200
150
100
50
0
Visit
Preop
Postop
0 1 2 3 4 6 8 12 24
Time after administration (h)


A
Roux-en-Y gastric bypass
B
Sleeve gastrectomy
Thrombin antithrombin complex (ng/mL)
Visit
Preop
Postop
Time after administration (h)
C
Roux-en-Y gastric bypass
D
Sleeve gastrectomy
Prothrombin fragments F1+F2 (pmol/L)
E
Roux-en-Y gastric bypass
F
Sleeve gastrectomy
D-dimers (ng/mL)

CLINICAL SIGNIFICANCE

- Recent ISTH guidelines have questioned the use of DOACs in obese patients. The recommendation was uniform for the DOAC drug class.
- Moreover, there are currently no recommendations regarding DOAC usage in patients who have undergone bariatric surgery.
- This review assessed the available evidence for rivaroxaban, and data retrieved indicate that its clinical profile is not affected by high body weight or bariatric surgery; hence, no dose adjustment is needed.